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Analgesics use and withdrawal in people with dementia – a register-based Danish study and a systematic review

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ABSTRACT

INTRODUCTION: Pain assessment in people with dementia is difficult, and withdrawal of analgesics may allow for assessment of treatment efficacy whilst decreasing pill burden, adverse events and interactions. We aimed to describe the use of analgesics among elderly in Denmark and to compile the evidence for withdrawal of analgesics among people with dementia.

METHODS: With respect to analgesics use, we employed data from national registries on the analgesic prescription use (opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen) in 2017 among elderly people with and without dementia. Trial evidence was produced by performing a systematic search in MEDLINE, Embase and Cinahl for trials evaluating withdrawal of analgesics in people with dementia.

RESULTS: Opioids were prescribed more frequently ($p = 0.026$) and NSAIDs less frequently ($p = 0.026$) to people with dementia. With respect to trial evidence, we identified two studies: An observational cross-over study ($n = 3$) reporting acetaminophen withdrawal leading to increases in pain frequency and duration, and a cluster-randomised clinical trial ($n = 352$) reporting changes in mobilization-observation-behaviour-intensity-dementia-2 (MOBID-2) pain score during a four-week withdrawal period (acetaminophen, opioids and/or pregabalin) from a mean \pm standard deviation of 2.3 ± 2.1 to 2.9 ± 2.6 compared with 3.5 ± 2.6 to 3.5 ± 2.5 in the control group.

CONCLUSIONS: In Denmark, use of opioids is higher in elderly with dementia compared to elderly without dementia. The evidence suggests that withdrawal of analgesics may aggravate pain but increases in pain scores may be of little clinical relevance in most people. Clinical trials investigating analgesics withdrawal are warranted.

KEY POINTS

- Use of opioids and acetaminophen is higher in elderly people with dementia than in elderly without dementia in Denmark.
- Evidence regarding deprescribing of analgesics among people with dementia is very limited but suggests that deprescribing of analgesics may precipitate behavioural symptoms and aggravation in pain in some but is an option for treatment evaluation.
- In many elderly people with dementia, analgesics may be withdrawn without clinically significant worsening in pain.

SYSTEMATIC REVIEW

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- 2) Indsatser for Rationel Farmakoterapi, The Danish Health Authority
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- 4) Danish Dementia Research Center, Rigshospitalet
- 5) The Dementia Clinic, Odense University Hospital
- 6) Department of Internal Medicine, Geriatric Section, Glostrup, Amager and Hvidovre Hospital
- 7) General practice, Lægerne i Græsted
- 8) Elderly Psychiatric Team, Region Nordjylland
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- 10) Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen, Gentofte Hospital, Denmark

relate to the difficulties of treating pain in people with dementia.

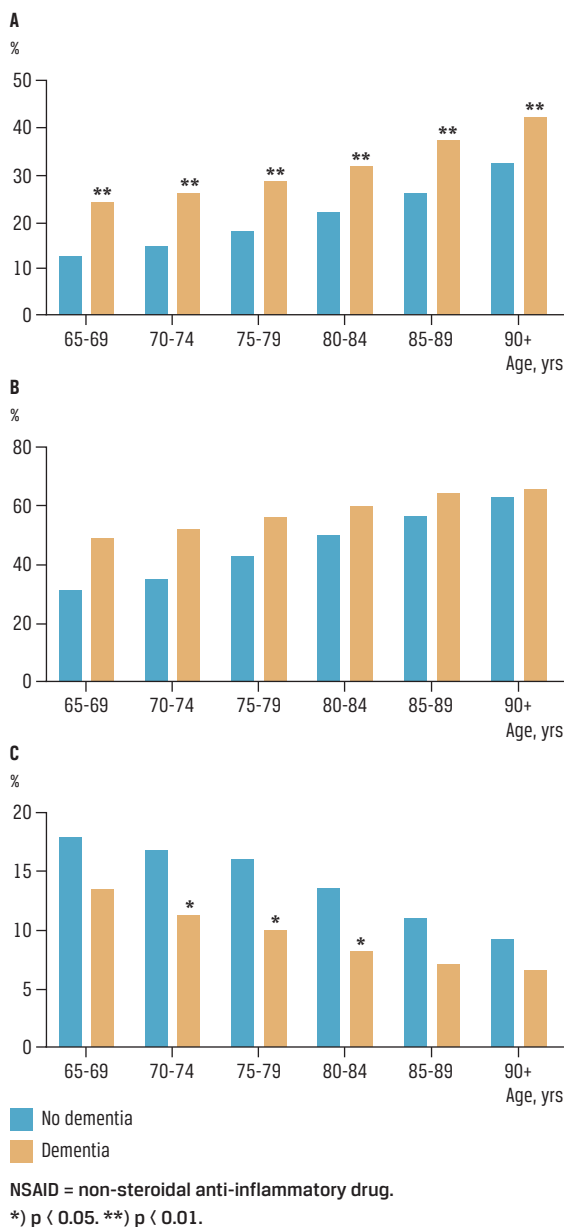
Dementia is a syndrome characterised by deterioration of memory and other cognitive functions, the ability to perform everyday activities and changes in overall behaviour. Dementia is usually progressive and occurs primarily in the elderly with a prevalence around 5-7% [3]. Ageing is often accompanied by pain-related comorbidities such as musculoskeletal disorders and cancer [4-6]. Due to the increasing life expectancy and the large birth cohorts after World War II, the number of people with dementia and painful comorbidities is expected to rise [4, 7].

Recent evidence has shown mixed findings on the use of analgesics among people with dementia [8-14]. A Danish register-based study found that among community-dwelling people, 28% of people with dementia and 17% of people without dementia received an opioid. The use of opioids was generally higher among nursing home residents, but slightly fewer nursing home residents with dementia (38%) were treated with an opioid compared with nursing home residents without dementia (43%) [8]. A Finnish study found a lower use of opioids among people with dementia than among those without dementia with an annual prevalence of opioid use of 3.56% and 4.62%, respectively (adjusted odds ratio 0.77, 95% confidence interval: 0.71-0.84) [12]. An Australian study among nursing

The Danish Ministry of Health published a nationwide dementia plan in January 2017 [1]. Among the initiatives were the publication of three national clinical guidelines. The author group all contributed to the guideline concerning dementia and medicine [2]. The present study is based on two PICO (population (P), intervention (I), comparison (C) and outcomes (O)) questions addressed in the guideline. These questions

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FIGURE 1 / Analgesic use among elderly with and without dementia. Patients with a prescription of opioid (A), acetaminophen (B) or NSAID (C) as percentage of population.



home residents showed no significant differences in analgesic drug use. Additionally, no significant differences in opioid use among people with or without dementia was found, 25% and 31%, respectively. However a significantly lower prevalence of oxycodone use among people with dementia was observed [14].

Pain is a fluctuating condition, and combined with the limitations in pain assessment among people with dementia, a once initiated treatment may continue for a long time without being questioned by a healthcare provider. However, if feasible, withdrawal of analgesics may allow for evaluation of efficacy and limit the risks

associated with polypharmacy such as drug interactions and adverse events. It has previously been described that withdrawal of antidepressants and antipsychotics is feasible in people with dementia [15, 16], but no systematic review has examined withdrawal of analgesics. Therefore, the aim of the study was a) to describe the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and acetaminophen among elderly people with and without dementia in Denmark and b) to identify clinical trials investigating the safety and efficacy of withdrawal of analgesics among people with dementia.

METHODS

Data for the study were gathered from two Danish registries and a systematic literature search. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline [17].

Data sources for epidemiological data

Epidemiological data were gathered linking diagnostic information with prescription redemptions from two Danish national registries; The Danish Register for Selected Chronic Diseases and Major Psychiatric Disorders and The Danish National Drug Prescription Register, using the unique civil registration number given to all Danish citizens at birth [18]. The population included all people with dementia on January 1 2017. People with dementia were defined as individuals who had a relevant diagnosis using the WHO International Classification of Diseases (ICD)-10 codes (F00, F01, F02 and F03) or who had redeemed at least two prescriptions of an ATC N06D drug. We excluded people with an unspecific dementia diagnosis (F03.9) and no redemption of an N06D drug and with no hospital contact registered during the past ten years.

Analgesics were identified in the prescription register using the Anatomical Therapeutic Chemical (ATC) classification. Included analgesics were NSAIDs (M01A), opioids (N02A) and paracetamol (N02BE). Data on analgesic use were gathered from January 1 2017 to December 31 2017. Users of analgesics were defined as people redeeming at least one prescription of that analgesic.

We stratified analgesic use according to age groups (65-69, 70-74, 75-79, 80-84, 85-89 and 90+ years).

Statistical analyses of epidemiological data

Standard descriptive statistics were applied to examine the association between analgesic use and dementia. The statistical analyses, unpaired t-tests and two-way ANOVA, were performed using Graphpad Prism, version 7 (GraphPad Software, La Jolla, CA, USA). A two-sided p-value < 0.05 was considered statistically significant.

Systematic literature search

The aim of the systematic literature search was to compile and review literature addressing withdrawal of analgesics in people with dementia. PICO-based questions concerning withdrawal of opioids and acetaminophen were determined prospectively (as part of a clinical guideline issued by the Danish Health Authority) [2] before the search was performed [19]. The systematic literature search was performed by a search specialist in accordance with the method description from the Danish Health Authority [19] and was divided into three steps; first we searched for guidelines, subsequently for systematic reviews and finally for randomised controlled trials. Reference lists of included articles were searched for additional studies. See for the detailed search strategies. The search strategy for guidelines was individualised for each database and is available upon request. The systematic search of MEDLINE, Embase and Cinahl was conducted from January to March 2018. The search strategy included terms synonymous with “opioid”, “acetaminophen” and “dementia”.

In all three steps, one author (AMSS) first screened the title and abstract, and in the next step three authors (AMSS, MBC and HP) screened the full-text papers. Disagreement concerning study eligibility was resolved by consulting another review author (EB). Data extraction was performed in duplicate by AMSS and EB.

Study selection

Studies were included if they fulfilled the following criteria: 1) Included people with dementia. All diagnoses of dementia were eligible. 2) The intervention included withdrawal of analgesics. Both abrupt and stepwise tapering was acceptable. Studies that were primarily treatment trials, but included a withdrawal period were also eligible for inclusion. 3) Only studies with publications in English, German or Scandinavian languages were included. There were no limits regarding publication year.

We excluded qualitative studies and studies with tapering, but not withdrawal of analgesics.

RESULTS

Analgesic use among people with dementia in Denmark in 2017

The use of opioids, acetaminophen and NSAID for people with and without dementia is presented in **Figure 1**. For people ≥ 65 years, the proportion prescribed an opioid was higher among those with dementia ($p = 0.026$). Stratified on age (65-69, 70-74, 75-79, 80-84, 85-89 and > 90 years), the association was statistically significant in all age groups. For people ≥ 65 years, the proportion prescribed acetaminophen was higher among those with dementia, though not statis-

tically significant ($p = 0.073$). The association was also not statistically significant in any of the aforementioned age groups. A different pattern was apparent for NSAID. For people ≥ 65 years, the proportion prescribed NSAID was higher among elderly people without dementia ($p = 0.026$). Stratified on age, the association was significant in three age groups (70-74, 75-79 and 80-84 years).

Identification of studies addressing withdrawal of analgesics in people with dementia

The initial search for guidelines yielded no relevant results. The search for randomised controlled trials and systematic reviews yielded two studies representing five published papers meeting the inclusion criteria (**Figure 2**). We did not identify studies directly investigating withdrawal of analgesics in people with dementia, but the two included trials contained withdrawal periods. Results are presented narratively due to the heterogeneity of the limited number of studies.

Results of studies addressing withdrawal of analgesics in people with dementia

Characteristics and results of the included studies are presented in **Table 1**.

Study 1 investigated the efficacy of acetaminophen on pain behaviours and included two baseline (no-treatment) phases [20]. The study lasted 24 days and included three people with a diagnosis of dementia and

FIGURE 2 / Flow chart for systematic reviews and randomised controlled trials.

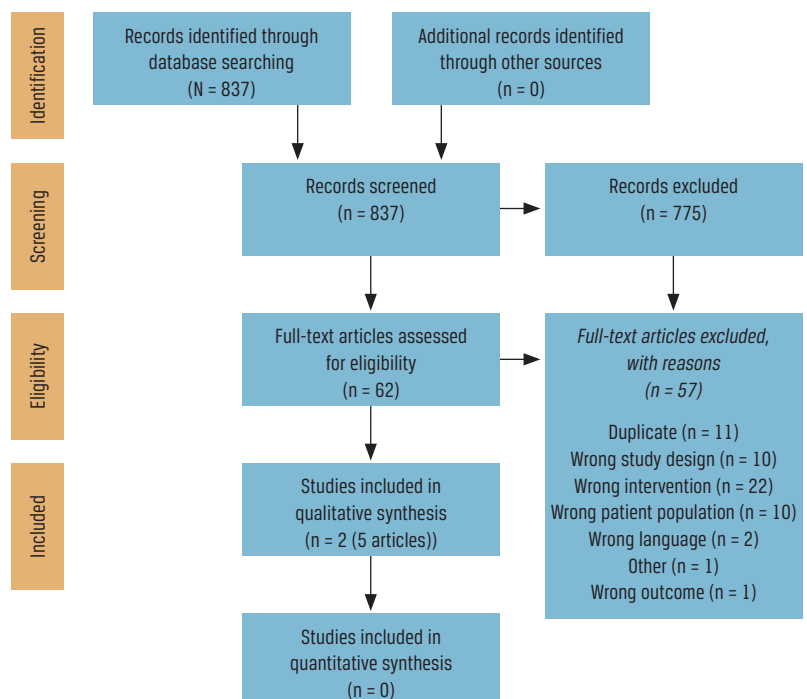


TABLE 1 / Clinical studies investigating withdrawal of analgesics in people with dementia.

Reference	Population	Design	Intervention	Comparison	Outcome measures	Findings
Elliot & Horgas, 2009, USA [20]	3 people living at home with a dementia diagnosis and a history of osteoarthritis	ABAB-single case-design over 24 days	Acetaminophen 1.3 g every 8 h during treatment phases Activity protocol during all phases	Activity protocol	Pain behaviour: frequency and duration, coded using the Noldus the Observer behaviour analysis software	Pain treatment led to decreases in the frequency and duration of pain Withdrawal led to the opposite
Husebo et al, 2011-2014, Norway [21, 22, 24, 27]	352 NH residents with moderate-severe dementia and agitation	Cluster-randomised trial over 8 wks with additional follow-up 4 wks after the end of treatment	Stepwise treatment approach with acetaminophen, morphine, buprenorphine and/or pregabalin	Usual treatment	CMAI, NPI-NH, MMSE, MOBID-2, ADL	CMAI and MOBID-2 scores increased from wk 8 to wk 12 in the intervention group The change was reported to be statistically significant regarding the latter

ABAB design = phases A and B are alternated; ADL = activities of daily living; CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination; MOBID-2 = Mobilization-Observation-Behaviour-Intensity-Dementia; NH = nursing home; NPI-NH = Neuropsychiatric Inventory - NH version.

a history of osteoarthritis (mean age: 85 years). During treatment phases, the participants received acetaminophen 1.3 g (two 650 mg tablets, extended release) every eight hours. The effect was assessed daily with an activity-based protocol consisting of normal activities of daily living, e.g. standing, sitting, walking. The activities were videotaped and coded by two raters. Data were reported for each participant individually. During treatment, the frequency and duration of pain behaviours decreased for all three participants. Furthermore, the frequency and duration of pain behaviours increased for all three participants when treatment was withdrawn. Whether the changes were statistically significant was not described.

Study 2 investigated a stepwise analgesic treatment approach among 352 nursing home residents with dementia and neuropsychiatric symptoms from 18 different nursing homes in Norway (mean age: control group 87 years and intervention group 85 years) [21-24]. The study was a cluster-randomised clinical trial lasting 12 weeks with the last four weeks being a withdrawal period. Participants randomised to active treatment received a stepwise treatment approach with initial acetaminophen followed by morphine, buprenorphine and/or pregabalin based on clinical evaluation of individual needs. Of 175 participants in the intervention group, 69% received acetaminophen, 2% received morphine, 22% received buprenorphine and 7% received pregabalin. Outcomes were measured at baseline and at weeks two, four, eight and 12. At baseline, 59% of the intervention group and 55% of the control group had a mobilization-observation-behaviour-intensity-dementia-2 (MOBID-2) score ≥ 3 , which is accepted as clinically relevant. The MOBID-2 scores increased from a mean (\pm standard deviation (SD)) of 2.3 (\pm 2.1) in week 8 to 2.9 (\pm 2.6) in week 12 in the intervention group (indicating an increase in pain). The change was reported to be statistically significant ($p = 0.022$). The

Cohen-Mansfield Agitation Inventory score increased from a mean (\pm SD) of 46.9 (\pm 18.7) in week eight to 50.3 (\pm 20.3) in week 12 in the intervention group (indicating an increase in agitation).

Quality of evidence

The two identified studies containing an analgesics withdrawal period among people with dementia were conducted in two different countries (United States and Norway) and were heterogeneous regarding study design, population, intervention and outcomes.

The results from the study by Elliott & Horgas should be interpreted with caution due to a high risk of bias [20] which included no blinding of participants, caregivers or the primary rater, who coded all videotaped protocols. In addition, the generalisability of the results is further limited by the very limited number of participants who all had a relevant pain diagnosis, were home dwelling and able to perform a daily activity protocol indicating a high performance status. The trial by Husebo et al had a low risk of bias. It was a randomised trial, which had measures in place to blind research assistants and caregivers, though the study was not placebo-controlled [21-24].

DISCUSSION

This review summarises the very limited published evidence describing the consequences of discontinuing analgesics in people with dementia and underlines that, in some people, withdrawal may precipitate behavioural symptoms and aggravation of pain.

The register data show a high use of opioids and acetaminophen among elderly with dementia in Denmark. Interestingly, the use of NSAIDs was higher among elderly without dementia than among age-matched people with dementia. In several countries, opioid prescriptions have increased during the past decades (though it has decreased in the United States

during the past years) and this might be part of the explanation for the observed high use of opioids [25, 26]. However, this cannot explain the discrepancy between elderly with and without dementia which, in turn, contrasts with some of the previous studies on analgesic use. The important point as to whether the substantial, and higher than average, use of analgesics among elderly with dementia reflects appropriate drug use remains uncertain and needs to be clarified.

In the study by Husebo et al, withdrawal of treatment resulted in a deterioration of mean values of both agitation and pain scores, which was statistically significant in the latter case. A previous study found that score changes in the MOBID-2 scale ≥ 3 were clinically relevant [27]. Therefore, the observed changes in the MOBID-2 score of less than one, albeit statistically significant, are likely not clinically relevant in most people. It is noteworthy that only 59% of the intervention group and 55% of the control group had clinically relevant pain scores (defined as pain scores ≥ 3 on the MOBID-2 scale) at baseline [21-24]. As results were presented for the entire intervention group, it remains unknown whether the effect of the intervention and withdrawal differs for the subgroups with and without clinically relevant pain scores at baseline. This seems likely though, taking into consideration the limited change in MOBID-2 scores and the rather large associated standard deviations (MOBID-2 scores increased from a mean (\pm SD) of 2.3 (\pm 2.1) in week eight to 2.9 (\pm 2.6) in week 12 in the intervention group). A lower effect on pain measures in people without relevant pain would be a reasonable assumption, and these are actually the ones in whom withdrawal may be most relevant.

The complex issue of treating pain in people with dementia has been reviewed several times. In a systematic review, Pieper et al included six studies that assessed pain interventions targeting behaviour in dementia [28]. Overall, the studies indicated that pain medication is effective in reducing pain and behavioural symptoms. In another systematic review, Husebo et al included eight studies that investigated the effect of analgesics on pain or behavioural symptoms [29]. The studies included treatment with acetaminophen, morphine, lidocaine and vitamin D. The authors emphasised the lack of evidence regarding pain management in people with dementia.

Strengths and limitations

The present study has several limitations. In the register-based part of the study, people with dementia were defined as individuals who redeemed at least one prescription of an ATC N06D-drug or who had a relevant diagnosis using the ICD-10 codes. It is possible that we underestimated the actual number of people

with dementia by using this definition. Furthermore, although a physician prescribed an analgesic and the prescription was redeemed, we have no information to establish if the drug was taken.

To our knowledge, this systematic review is the first concerning withdrawal of analgesics among people with dementia. We performed thorough searches for publications in all major medical databases. Nevertheless, the very limited number of identified trials, including one with a very small sample size, and the low quality of evidence severely limits the conclusions that may be drawn about withdrawal of analgesics in people with dementia. As the use of opioids has been increasing worldwide, we believe that our findings are applicable outside Denmark. This review highlights the need for further research to clarify the consequences of discontinuing analgesics in people with dementia.

CONCLUSIONS

Use of opioids in Denmark is higher in people with dementia than in an age-matched population without dementia. It remains unclear whether the substantial use of opioids among people with dementia in Denmark reflects appropriate pharmacotherapy. The evidence regarding withdrawal of analgesics among people with dementia is very limited but suggests that although withdrawal may precipitate behavioural symptoms and worsening in pain in some, it is an option for treatment evaluation and deprescribing in many.

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